REJUVENATION AND THE PROLONGATION OF LIFE: SCIENCE OR QUACKERY?

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Across the ages, human beings have tried to prolong life and evade senility by magical, religious, and scientific means. In modern times, the role of science has naturally been preeminent. For a time during the early decades of this century, scientists indeed seemed to have discovered a number of methods to conquer senility. Appearances, unsurprisingly, were deceptive, and the entire episode was soon forgotten. Neither scientists nor historians have devoted much attention to the topic, and only a few historical studies are available [1–2]. Contemporary scientists or physicians think of this subject, if at all, as part of the history of quackery or, at best, of the gullibility of scientists.

Closer historical examination reveals this view to be simplistic. To be sure, rejuvenation research had its share of cranks and charlatans. Even the serious scientists in the area were frequently unsound in their methods and drew hasty, wish-fulfilling conclusions. It is unfair, however, to overlook that these flaws notwithstanding, much of this research was conceived along accepted scientific doctrine *of the time*. The history of rejuvenation research, like the history of science in general, reveals a complex interplay of rationality, gullibility, and sheer folly.

I shall establish these contentions by examining the independent efforts of a biologist, an experimental physiologist, and a fashionable surgeon to retard or reverse human aging. The biologist is Elie Metchnikoff [Il'ia Il'ich Mechnikov] (1845–1916), the experimental physiologist is Eugen Steinach (1861–1944), and the surgeon is Serge Avramovitch Voronoff (1866–1951).

I shall argue that Metchnikoff and, to a lesser extent, Voronoff approached the problem of senility from the standpoint of evolutionary

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biology. Their ideas on the subject will be contrasted with those of Steinach, whose approach was unrelated to evolutionary thought. In my analysis of this aspect of their work, I shall draw upon a dichotomy popularized by biologist and historian Ernst Mayr. Mayr argues that the biological sciences are generally divisible into those that deal with proximate phenomena and those that investigate ultimate causes [3]. Mayr uses the terms as disciplinary distinctions, physiology being the prototype of the former and evolutionary biology of the latter. I feel, however, that the distinction can also be of help in identifying differences of conceptual level *between* theories in one field as well as *within* the apparently homogeneous thought of individual biologists.

Metchnikoff: Senility, Microbes, and Sour Milk

Elie Metchnikoff shared the 1908 Nobel Prize in physiology or medicine with Paul Ehrlich for his research on inflammation and the immune response. His work in these fields has been explored in detail by historians and immunologists [4–6]. Metchnikoff's ideas on the prevention of senility, however, have been treated superficially in these studies. This is unfortunate since Metchnikoff's studies on aging were grounded in his biological beliefs and constitute an excellent historical example of the use of evolutionary principles to solve a physiological problem.

Metchnikoff's biological philosophy revolved around the twin notions of "harmony" and "disharmony." Disharmony, for Metchnikoff, was the central fact of life. Any anatomical feature that did not serve a clear and important function was an instance of disharmony. Organisms, especially humans, were fundamentally disharmonious in structure and function. Metchnikoff blamed this on the evolutionary process itself, which moved by piling one ad-hoc modification on another. Living forms, instead of being examples of perfect design, were jury-rigged from diverse, ill-adjusted components. At the best of times, the components managed to act together with some efficiency. More often, they did not [6].

Metchnikoff believed that evolution would, in the dim future, iron out all biological disharmonies. But the natural tempo of evolution being excruciatingly slow, the process needed to be speeded up by "science." Science was a harmonizing, ameliorative force, and the only effective weapon against disharmony. All these themes—present disharmony, future harmony, and the role of science in expediting the latter—came together in Metchnikoff's studies on human aging.

Metchnikoff's crowning example of biological disharmony was the human large intestine. Our evolutionary ancestors needed it, said Metchnikoff, because they were small, herbivorous animals living on predator-infested grasslands. The large gut itself was needed to store

feces (to stop for defecation was to attract predators), and its microflora was necessary for digesting the cellulose-rich diet. Human beings no longer required these services but, thanks to the slowness of evolution, the coils of the large gut still cluttered their abdomen. The large intestine was not just useless, it was an inexhaustible source of poison. Its microbial flora secreted toxic products into the bloodstream and poisoned humans into senility and premature death [7].

Metchnikoff regarded the features of human senility as consequences of a single histologic process. This was *"the atrophy of the higher and specific cells of a tissue and their replacement by hypertrophied connective tissue"* [7, p. 238, Metchnikoff's italics]. The specialized cells of the major organs (such as the nerve cells in the brain, or the hepatic cells in the liver) declined in number and function with age. As they atrophied, their place was taken by connective tissue. Being functionally unspecialized, the latter could not effectively substitute for the atrophied cells. The vital functions of the organism thus underwent global decline in old age.

The replacement of the higher cells by the lower was the outcome of conflict. "The word conflict," Metchnikoff emphasized, "is not used metaphorically in this case. It is a veritable battle that rages in the innermost recesses of our beings" [7, p. 239]. The battle was between the higher cells and the cells that, in other contexts, defended the body against infections and cleared the debris of biological processes: the phagocytes. As an individual aged, the phagocytes became hyperactive and began to attack the most important cells of the body. Having destroyed the higher cells, the phagocytes produced connective tissue to fill up the vacant spaces.

Neither natural nor inevitable, senility was the consequence of biological civil war. Life could be prolonged if the war could be halted. What, however, was the natural human life span which would end in natural death? Instead of providing a clear answer, Metchnikoff made an interesting suggestion. He felt that the human instinct for self-preservation should disappear after completion of the natural life span. At this point, individuals would cease wishing to live and an "instinct of death" would take over, leading them to welcome extinction. Metchnikoff coined the term "orthobiosis" to denote this natural cycle of life [7].

How could the orthobiotic cycle be realized? How could old age be freed of senility? Since senility was the result of a conflict between higher and lower elements of the body, one could either strengthen the former or weaken the latter. Alcohol and substances such as lead or mercury had to be avoided since they accelerated senile atrophy by weakening the higher cells and leaving the phagocytes relatively unaffected [7]. Metchnikoff was, however, not very confident that other practicable ways to protect the higher organs would be available in the near future.

Another approach was to control the unruly phagocytes. Metchnikoff suspected that toxic principles from the large intestine were absorbed by the blood and induced the phagocytes to attack the higher organs. Evidence of this continuous intoxication was available in the urine. Derivatives of phenol, indol, or skatol were detectable in the urine *except* when the large intestine was somehow inactive. Metchnikoff based this claim on just one study which he did not even cite in full [7].

Among the intestinal microbes, the anaerobic strains were the most dangerous. These caused putrefaction and butyric fermentation, which produced the toxins inducing senile atrophy. Dietary measures were a good first step toward preventing these two processes. Uncooked food and raw vegetables, which introduced fresh anaerobic microbes into the intestine, had to be avoided completely.

The consumption of cooked food and boiled liquids could not, however, destroy the putrefactive microbes that were already present in the gut. One possible way to do this was by acidifying the intestinal contents [8]. Metchnikoff felt that milk was the agent of choice. It went sour with ease due to fermentation by lactic acid-producing microbes. These microbes, so to speak, were good microbes. By generating acid, they prevented putrefaction. They could, therefore, be used for intestinal acidification. Administration was not a problem. Consuming sour milk or products made from it would be adequate.

Such products had long been poular in many cultures. The Tartars and the Kirghiz drank *koumiss* while *kefir* was popular among some Caucasian tribes. The Egyptians had their *leben* and the Bulgarians their *yahourth.* These traditional preparations, however, were either too impure or otherwise unsuitable for regular consumption [8]. Metchnikoff's specific against senility was prepared under stringently hygienic conditions. Boiled milk was curdled with pure cultures of lactic acid bacilli [8]. The product had to be consumed in doses between three hundred and five hundred cubic centimeters daily to prevent intestinal putrefaction.

This recipe soon attracted the interest of a commercial manufacturer. Metchnikoff permitted his name to be used in advertisements for the product, which led to baseless accusations that he was making money out of his "discovery." The scientific community does not seem to have taken up Metchnikoff's theory for serious investigation. Metchnikoff himself did not conduct experimental studies with sour milk except on his own person. From the age of fifty-three until his death at seventy-one, he assiduously followed his own regimen [9].

He had begun to "treat" himself from 1898, after his physician had diagnosed a moderate degree of arteriosclerosis. Over the next eighteen years. Metchnikoff struggled to convince himself that his program was retarding senility. This was difficult since he was often seriously ill dur-

ing the last years of life. Conceding that he had failed to achieve full orthobiosis, Metchnikoff pointed out that the results would have been better had he commenced the regimen earlier in life [9].

Metchnikoff could not forget, let alone forgive, his large intestine even on his deathbed. His last recorded words, addressed to his physician, were: "You remember your promise? You will do my postmortem? And look at the intestines carefully, for I think there is something there now" [9, p. 273].

Steinach and Voronoff: The Sex Glands as Fountains of Youth

Metchnikoff had been dead for only about four years when "rejuvenation" became a hot medical subject. The focus of interest, however, now shifted to the sex glands, particularly the testes. There was at least one well-known precedent for this trend. The French-American physiologist Charles-Edouard Brown-Séquard had claimed in 1889 that he had rejuvenated himself by subcutaneous injections of testicular extracts. Brown-Séquard's report had stimulated much serious endocrinological research, and also inaugurated the *fin de siècle* craze for "organotherapy" [10–12].

Much of this excitement had abated by the 1920s. Memories of Brown-Séquard were, however, rekindled by the claims of Eugen Steinach and, a little later, of Serge Voronoff that the sex glands could indeed be used for rejuvenation, albeit not by methods as simple as Brown-Séquard's.

Steinach had begun his research career in physiology at the University of Prague and, in 1912, became the director of the Biological Institute of the Viennese Academy of Sciences, popularly known as the Vienna Vivarium [13–14]. From 1910, Steinach had begun to investigate the physiology of the sex glands. He conducted many elegant experiments demonstrating the role of the sex glands in determining anatomical sex-characteristics, psychosexual orientation, and sexual behavior [15].

Many of these experiments involved the castration of animals. Steinach noticed that young castrates underwent anatomical, physiological, and behavioral changes that were almost identical to senility. Some of those features were loss of appetite and weight, dullness or even partial loss of fur, lethargy, sluggish movements, and unsteady gait [16]. These changes, Steinach further noted, were reversed after testicular reimplantation.

Steinach did not believe that the *reproductive part* of the gland was responsible for the reversals, since it degenerated soon after implantation. The interstitial cells, however, remained active. Steinach collectively designated the interstitial cells as the *puberty-gland* since he believed them to trigger the onset of puberty. The hormones of the

"puberty-gland" determined sexual orientation, sustained erotic interest, and governed the functions of the internal and external genitalia [15–16].

Steinach made a further striking observation concerning the reversal of postcastration changes. Castrated animals subjected to reimplantation of sex glands often become hypermasculine or hyperfeminine. (The evaluation was made on the basis of a number of anatomical and behavioral criteria, of which the size of the seminal vesicles, Steinach felt, was the most reliable.) Steinach attributed this phenomenon to the degeneration of the reproductive part of the transplanted gland and consequent hypertrophy of the "puberty-gland."

Castration and reimplantation were not the only ways to bring about hypermasculinity or hyperfemininity. The functions of the "puberty-gland," Steinach argued, could be augmented even in an intact animal simply by inducing degeneration of the reproductive part of the gland. The similarities between castrates and the senile encouraged Steinach to regard senility as a state of functional castration. Since the tissues and organs of the body that showed involution after castration revived after transplantation of sex glands, it seemed likely to Steinach that senile involution could be reversed by stimulating the senile organism's "puberty-gland" [16].

Why not try to bring this about by eliminating the reproductive part of the gland? The easiest way of doing this in the intact male animal was by resecting the spermatic duct between ligatures. Spermatic secretions would then accumulate within the reproductive part of the sex gland and induce pressure atrophy of the reproductive cells. This atrophy would, in turn, induce the hypertrophy of the "puberty-gland."

In female animals, this procedure was obviously inapplicable, and Steinach suggested that the germinal portions of the ovary be extirpated by low doses of X-rays. The "puberty-gland" of the ovary, he believed, was less radiosensitive than the reproductive part. Thus, the X-rays would elminate the latter, leaving the former intact. As in the case of males, the mere removal of the reproductive part would bring about spontaneous hypertrophy of the "puberty-gland" [16].

Steinach claimed that his methods were completely successful in laboratory rats. Within three to four weeks after vasoligation, formerly senile rats became active and even aggressive. Sexual interest reawakened, and appetite was regained. There was rapid gain in weight, and the animal became vigorous and youthful in appearance. At autopsy, the muscles and internal organs were found to be well-nourished and flushed with blood. The dimensions of the internal reproductive organs (particularly Steinach's yardstick organ, the seminal vesicle) were as in young adult specimens of the same species [15]. There was no hypermasculinization or hyperfeminization; merely optimal sexualization. Steinach did not

explain why this should be the case if senility was a condition of functional castration.

Steinach was so impressed by his rat experiments that in 1918 he persuaded the urologic surgeon Robert Lichtenstern to try vasoligation on senile humans. A forty-three-year-old coachman was the first subject. He was, of course, too young to be considered senile, but his complaints suggested a premature onset of the process of senile involution. On examination, there was no evidence of any systemic illness and no contraindication to the relatively minor operation.

Within three months after the operation, the patient's appetite improved, he gained weight, his skin became smooth and supple, and there was fresh growth of body hair. Eighteen months after the operation, all these improvements were maintained, and the patient led a vigorous, energetic life. Lichtenstern went on to perform some four hundred "Steinach operations." Numerous surgeons all over the world shared in the "Steinach Wave" of the 1920s and 1930s [17].

Positive results were reported in almost all the cases. Among the many people who chose to have a Steinach operation were Sigmund Freud [13] and the poet W. B. Yeats [18]. There was also much criticism of Steinach's rat experiments as well as of the operations on humans. The diagnosis of senility itself raised serious questions. Were Steinach's rats really suffering from senile hair loss, or were they just mangy? Many who agreed with Steinach's explanation of senility nevertheless felt that the operation would accelerate senile decay after a short period of apparent rejuvenation. Application of the technique to human beings was condemned by some as unnatural or even immoral. Finally, and perhaps most pertinently, many opponents of the operation believed that it produced its effects solely by suggestion [19].

Even in its heyday, the Steinach operation was often confused with another rejuvenative technique: monkey-gland transplantation. This colorfully named procedure involved the grafting of testicular tissue from chimpanzees or baboons in senile humans. While many surgeons of the period experimented with testicular grafting, the use of monkey glands was the innovation of Serge Voronoff of Paris. Born in 1866 in Voronezh, Russia, Voronoff emigrated to France when he was eighteen. He trained in medicine and worked for some years in Egypt as a physician to the Court of Khedive Abbas II. In 1910, he returned to Paris and set up a fashionable surgical practice. At about the same time, he began to experiment with organ transplantation. He claimed successful transplantation of the thyroid gland of an ape in a cretinous child of fourteen. Then, during World War I, Vornoff joined the French army and acquired considerable experience in bone grafting on wounded soldiers [20].

In 1917, Vornoff resigned from the Army and managed to find a

position as a researcher at the prestigious Collège de France. From now on, Voronoff's work would be concerned solely with aging and its reversal. He claimed to have rejuvenated senile rams by transplantations of testicular tissue from young rams. In 1920, he felt confident enough to transplant chimpanzee testicles on two men who had lost their testes due to tuberculosis. Both cases were unsuccessful, but Vornoff did not give up. Soon, he began to claim excellent results from the transplantations and boasted that monkey-gland transplants could "put back human aging by twenty to thirty years."

Monkey-gland transplantation, like the Steinach operation, was applicable to men alone. Both Steinach and Voronoff hoped that a method for female rejuvenation would be discovered in the future, and Steinach, of course, even suggested the use of low-dose radiation. However, interest in female rejuvenation remained negligible. Voronoff acknowledged the difficulties and remarked:

> In the meantime I can only offer this consolation: the mortality statistics of every land prove that women live much longer than men. Hence they already have the advantage of us and consequently may still wait a few more years before the experiments in course of development bring them the remedy which is to intensify and prolong their existence [21, pp. 116–117].

Monkey-gland treatment, expectedly enough, faced severe criticism from many physicians and surgeons. Eugen Steinach considered the technique to be worthless. Testicular grafts, he claimed, were accepted by the body only if the host was a bilateral castrate. Existing gonads, no matter how weak or how senile, would always resist the implanted gonads and bring about their rejection. And the rejection would be all the swifter if the implanted tissue was from another species.

Without explaining how or why the rejection occurred, Steinach declared, "It amounts to self-delusion if people seriously believe that the transplantation of chimpanzee testicles into human beings can produce anything but rapidly passing effects" [15, pp. 81–82]. Popular interest in monkey-gland treatment, however, was unaffected by professional criticism. Much of this interest was nurtured by Voronoff's sophisticated handling of the media and his lucid, persuasive books on the subject.

Metchnikoff, Steinach, Voronoff: Parallels and Divergences

Metchnikoff's immunological model of senility may have failed to enthuse scientists, but Serge Voronoff discussed it with great respect. Voronoff agreed that senility resulted from the phagocytic destruction of the higher cells and their subsequent replacement by connective tissue. However, he considered the endocrine glands to hold the key to senility. The endocrine hormones, according to Voronoff, energized and pro-

tected the higher cells from destruction. The endocrine glands themselves, however, were not immune to phagocytic attacks. Glandular function, therefore, declined with time, and senility could be vanquished only if the endocrine glands were somehow revitalized.

For Voronoff, the most important endocrine glands were the testicles. Steinach's research on rejuvenation began with the observation that castrated animals showed changes indistinguishable from the features of senility. Voronoff proffered the same analogy but referred it to his observations of human eunuchs while in Egypt. After portraying eunuchs as prematurely senile, Voronoff declared, "In the manifestation of his physical and intellectual qualities, varying according to the individual, man himself is worth whatever his sex glands are worth" [21, p. 58].

Steinach would probably have applauded this statement but not the Metchnikoffian pathology on which Voronoff's view of senility was based. Steinch did not believe that senility implied any significant destruction of organs or specialized cells. They became nonfunctional in old age simply because of suboptimal blood circulation and consequent undernutrition. The sex hormones were responsible for maintaining circulation. As soon as the hormones began to flow again, blood circulation improved, the tisues were perfused with adequate amounts of nutritive substances, and the "senile" tissues regained their functions [19].

Both Steinach and Voronoff considered the reproductive part of the sex gland to be unimportant for rejuvenation. Their methods for replacing or supplementing the endocrine part were, of course, very different. Steinach consistently believed that the proper stimulation would revitalize any organ. For all organs except the sex glands, stimulation involved augmentation of blood flow. This augmentation, of course, could be achieved only by enhancing the secretion of sex hormones. As for the sex glands themselves, the elimination of the reproductive element resulted in sufficient stimulation of the "puberty-gland."

Voronoff did not believe in stimulation but in replacement. His understanding of the pathology of senility could hardly allow him to do otherwise. However, the very belief that lost functions were at least partly regained after transplantation indicates that Voronoff's theory still harbored some self-contradictory faith in regeneration. How, one wonders, could a senile organism become revitalized if its higher cells had already been replaced by connective tissue?

It might be instructive to recollect Metchnikoff's stance on this subject. He certainly believed that life could be prolonged by controlling intestinal microbes. But his viewpoint was always one of preventive hygiene. Treatment with sour milk had to begin from infancy if complete orthobiosis was to be achieved. Lost tissue could not be replaced, nor arteriosclerosis reversed, by all the sour milk in the world. It was worth-

while to begin treatment at any age, but in adults all that could be done was to prevent further tissue destruction.

Evolutionary biology, we have already seen, played an important role in Metchnikoff's views on life, aging, and death. Voronoff utilized evolutionary notions too, but in an interestingly different way. While defending the use of monkey glands for human grafting, Voronoff acknowledged that, theoretically, grafts should be obtained only from human donors. But this was not a practical proposition. The few men who were willing to do without one testicle expected exorbitant payment for the gland. Removal of testicles from fresh cadavers was possible but illegal. It was also illegal to obtain the glands from criminals condemned to death.

The solution lay in the intimate evolutionary links between humans and the anthropoid apes (the orangutan, the chimpanzee, and the baboon). Embryologically, anatomically, and physiologically, humans bore remarkable similarities to these higher simians. Even human blood, remarked Voronoff, "is absolutely similar to that of these apes and differs completely from that of any other animal." Humans and anthropoid apes were even prone to some diseases like typhoid or syphilis from which all other animals were immune [21].

Thus, it seemed clear to Voronoff that "the organ of an ape transplanted into the body of a man will find there the same conditions of life, the same nutrition available in the case of its first host, and that it will be able to adapt itself to its new existence amid these surroundings with which it is familiar." Grafts from other kinds of animals were *not* permissible because the donors in this case were too widely separated from humans [21, pp. 92–93]. Today, the phrase "monkey-gland treatment" evokes an image of the most irresponsible quackery. For Voronoff, however, it was a therapeutic choice made according to what he considered to be sound biological principles.

For Metchnikoff, evolutionary disharmony was the ultimate cause of senility. For Voronoff, evolutionary relationships provided the solution to the problem of senility. Steinach, however, remained rooted in individual bodies and did not use evolutionary biology to frame the problem of senility or to solve it. An experimental scientist par excellence, he was preoccupied with determining what went wrong in the body and what could be done to set it right.

To put the issue in Ernst Mayr's terminology, Metchnikoff's central hypothesis was one of ultimate causes. Both Steinach and Voronoff, on the contrary, worked on the basis of hypotheses concerned with proximate factors. Steinach's rejuvenative technique, too, was based on proximate principles while Voronoff's was based on ultimate, evolutionary ones.

If evolutionary theory did not exist, Steinach's theory or his practice

need not have been any different. Nor would Voronoff's causal hypotheses have needed revisions in such a situation. His rejuvenative procedure, however, could not have existed without the idea of common descent of humans and anthropoid apes. Metchnikoff's theory *and* his practice would have been annihilated if their evolutionary scaffolding had been removed.

The history of research on aging and its prevention, therefore, is not simply a story of quackery. Nor, of course, does it fit the stereotype of science as a purely rational activity. It is more realistic (and rewarding) to view it as a very human phenomenon, in which the fear of old age and death interacted with the modernist faith in science to open a strange but not necessarily irrational field of research.

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THE "POP" QUIZ

Said the professor with a smile on his face,
"Here's a disease of profound distaste.
Let's play a little game, give me the cause and the name,"
And he presented the following case:

"Our patient is a child of eight,
and we fear a short life is her fate.
Her mind is a mess, and her urine has excess
heparan and dermatan sulfate."

"This situation is clearly atrocious,"
said our student who was somewhat precocious.
"An enzyme's gone loco, and the disease is a muco-
polysaccharidosis."

BARRY T. PETERSON